REMARKS

The previously raised Section 112, first paragraph rejection and Section 103 rejection (based on Valone *et al.*, in view of Press *et al.* and Natali *et al.* and further in view of Burton *et al.*) are withdrawn. The Examiner raises new Section 112, first paragraph and Section 103 rejections, which are addressed below.

Amendments

Claims 26 and 43 are amended herein, with support for the "200-600 mole" range found on at least page 20, line 25. Typographical errors in claims 29 and 45 are corrected herein. Claim 37 is amended to add back the "colon" cancer indication previously deleted from the claim. Claim 39 is amended so as to depend on claim 37. Claims 37 and 42 and revised herein to include the recitation "the formulation comprises the antibody and a lyoprotectant, wherein the molar ratio of lyoprotectant:antibody is 100-600 mole lyoprotectant:1 mole antibody," with support for this amendment found in at least claim 26 and on page 20, lines 23-25.

In that the amendments do not introduce new matter, entry thereof is respectfully requested.

35 USC Section 112, first paragraph, new rejection

Claims 26, 28-34 and 37-51 are rejected under 35 USC Section 112, first paragraph on the basis that the specification, while being enabling for a method of treating cancer comprising the administration of rhuMAb HER2 (Herceptin®), does not reasonably provide enablement for a method of treating cancer with any HER2 antibody. The Examiner urges that while the art does provide ample evidence that certain HER2 antibodies (Herceptin®) are effective in treating cancer, it has not taught that all HER2 antibodies are effective in treating cancers by inhibiting cell growth. The Examiner relies on Stancovski *et al. PNAS USA* 88: 8691-8695 (1991) as teaching that while some anti-ErbB2 antibodies inhibit tumor growth, at least one of the antibodies

actually accelerated tumor cell growth.

Applicants submit that the invention set forth in claims 26, 28-34 and 37-51 was enabled by the present specification at the time of filing.

The present application enables therapy of endometrial, lung, (colon) and bladder cancer, as well as ductal carcinoma *in situ* (DCIS) with an antibody which binds HER2 receptor (specification at page 24, lines 11-16; and Example 1 on pages 25-37, for instance). While huMAb4D5-8 (Herceptin®) is exemplified, the specification clearly teaches therapy with other antibodies that, like Herceptin®, will be therapeutically effective in treating endometrial cancer, lung cancer, (colon cancer) bladder cancer, or DCIS as claimed in the present application (specification at page 24, lines 11-16, for example). The art at the time of filing taught that anti-HER2 antibodies other than 4D5/Herceptin®, against various HER2 epitopes, could inhibit the growth of cancer cells expressing HER2. See, for instance, Tables I and II of Shepard *et al. J. Clin. Immunol.* 11(3):117-127 (1991)(of record) which reference growth inhibitory anti-HER2 antibodies 3E8, 7F3 and 3H4, for example. See, also, US Patent No. 5,677,171 (Hudziak *et al.*, filed January 12, 1988; of record) which describes antibodies 3E8 and 3H4 that inhibit growth of cancer cells expressing HER2 (Fig. 3 of Hudziak *et al.*) and reports that 3E8 "gives 100% tumor growth inhibition" in an *in vivo* tumor model (Hudziak *et al.* at column 19, line 34). Hence, Applicants submit that the present specification combined with the art at the time the above application was filed enabled the presently claimed invention for antibodies including, but not limited to, 4D5/Herceptin®.

Addressing now the Examiner's reliance on Stancovski *et al.*, Applicants submit that this publication would not have eroded, in the mind of the reasonably skilled medical practitioner, the credibility of using various anti-HER2 antibodies, including 4D5, Herceptin®, 3E8, 7F3 and 3H4, for instance, in the presently claimed methods. Since

the present application teaches administration of an antibody which treats or prevents cancer (specification at page 24, lines 11-16), the skilled artisan was taught to use a therapeutically effective anti-HER2 antibody, rather than an antibody like Stancovski's N28 antibody that accelerated tumor cell growth. ↳ but no regulation

In sum, Applicants submit that the objective evidence in the form of Shepard *et al.* and Hudziak *et al.* as discussed above, combined with the disclosure of the present specification demonstrates that the presently claimed invention was enabled by the specification at the time of filing. Reconsideration and withdrawal of the Section 112, first paragraph rejection is respectfully requested in view of the above.

35 USC Section 103, new rejection

Claims 26, 28, 37-43 and 51 are rejected under 35 USC Section 103(a) as being unpatentable over Shepard *et al. J. Clin. Immunol.* 11(3):117-127 (1991); in view of Draber *et al. J. Immunol. Methods* 181(1): 37-43 (1995); Sato *et al. Cancer* 70(10): 2493-8 (1992); Nielsen *et al. Am. J. Clin. Pathol.* 102(1):76-9 (1994); Natali *et al. Int. J. Cancer* 45:457-461 (1990); and Roy *et al. Dev. Biol. Stand.* 74:323-329 (1992).

The Examiner relies on Shepard *et al.* as teaching that an antibody, 4D5, can inhibit cell growth when HER2 is overexpressed in tumor cells, such as breast, ovarian, and lung carcinomas; and that 4D5 can be used for treating tumors that overexpress HER2 protooncogene. The Examiner states that Shepard *et al.* does not specifically teach HER2 expression in endometrial, bladder or colon cancer, or in ductal carcinoma *in situ*, and does not specifically disclose a formulation wherein an antibody is lyophilized in the presence of lyprotectants. Nielsen *et al.*, Sato *et al.* and Natali *et al.* are relied on as teaching the expression of HER2 in endometrial cancer, bladder cancer, colon cancer and ductal carcinoma *in situ*, respectively. Draber *et al.* is referenced as teaching lyophilizing an antibody, wherein trehalose

is used as a lyoprotectant, and that such an antibody can be stored for a long time at ambient temperatures. Roy *et al.* is cited as teaching that antibody formulations can contain glycine and mannitol as useful bulking agents in freeze-dried preparations of antibodies.

The Examiner urges that it would have been *prima facie* obvious at the time the invention was made to treat cancer, especially endometrial cancer, bladder cancer, colon cancer, lung cancer, or ductal carcinoma *in situ*, by administering a formulation comprising an antibody, 4D5/Herceptin®, lyophilized in the presence of a lyoprotectant and bulking agent.

Applicants submit that the invention set forth in claims 26, 28, 37-43 and 51 is patentable over the cited art.

Claim 37, as amended herein, pertains to a method for treating a cancer selected from the group consisting of endometrial, lung, colon, and bladder cancer in a human comprising administering a therapeutically effective amount of a formulation comprising an antibody which binds HER2 receptor to the human, wherein the formulation comprises the antibody and a lyoprotectant, wherein the molar ratio of lyoprotectant:antibody is 100-600 mole lyoprotectant:1 mole antibody. Claim 42 herein concerns a method for treating ductal carcinoma *in situ* in a human comprising administering a therapeutically effective amount of a formulation comprising an antibody which binds HER2 receptor to the human, wherein the formulation comprises the antibody and a lyoprotectant, wherein the molar ratio of lyoprotectant:antibody is 100-600 mole lyoprotectant:1 mole antibody.

Applicants submit that claims 37 and 42 (and the claims which depend thereon) are patentable over the cited art. In particular, Applicants submit that treating the recited cancers or DCIS with a anti-HER2 antibody formulation, wherein the molar ratio of

lyoprotectant:antibody is 100-600 mole lyoprotectant:1 mole antibody, was not obvious from the cited art. As explained on page 2, lines 21-24 of the specification, in spite of the use of lower concentrations of the lyoprotectant relative to the anti-HER2 antibody (*e.g.* as recited in claims 37 and 42 as amended), it was discovered that the anti-HER2 antibody in the lyophilized formulation essentially retained its physical and chemical stability and integrity (see Example 1 on pages 25-37). The present specification describes various anti-HER2 antibody formulations having the claimed molar ratio of lyoprotectant: antibody (see Example 1 and elsewhere in the specification); and therapy of endometrial cancer, lung cancer, colon cancer, bladder cancer, or DCIS with such formulations (page 24, lines 11-16, for instance).

While the Examiner urges that, in the absence of evidence to the contrary, the recited molar ratio would be considered to be "routine optimization" of the formulation in Draber *et al.*, Applicants will demonstrate here that this is clearly not a case of routine optimization of Draber's teachings.

First, Draber *et al.* are concerned with monoclonal IgM antibodies in pre-aliquoted kits used for immunoassays (abstract and last sentence of the Discussion of Draber *et al.* on page 42). Draber *et al.* is not concerned with an anti-HER2 antibody formulation for therapy of endometrial cancer, lung cancer, colon cancer, bladder cancer, or DCIS in human patients.

Moreover, Draber *et al.* teaches away from the presently claimed low molar ratio (100-600 mole lyoprotectant: 1 mole antibody) in claims 37 and 42 herein.

Draber *et al.* refers to freeze-drying IgM supernatants (5-50µg/ml IgM antibody) or ascitic fluid (1-15 mg/ml IgM) (see page 40 of this reference). Page 39 of Draber *et al.* states that the concentration of

trehalose was routinely 0.25M. Assuming a 950,000 molecular mass for the IgM pentamer, the molar ratios of trehalose to IgM are as follows.

Trehalose:IgM in Draber *et al.*	**Molar ratio**
0.25M trehalose: 5 µg/ml IgM	$4.7x10^7:1^a$
0.25M trehalose: 50 µg/ml IgM	$4.7x10^6:1^b$
0.25M trehalose: 1/mg/ml IgM	$2.4x10^5:1^c$
0.25M trehalose: 15/mg/ml IgM	$1.6x10^4:1^d$

(a) 5 µg/mL = 0.005 g/L which after dividing by 950,000 g/mole = $0.53x10^{-8}$ M. Thus 0.25 M trehalose/$0.53x10^{-8}$ M IgM= $4.7x10^7$. (b) Then for 50 µg/mL, the ratio is $4.7x10^6$. (c) IgM at 1 mg/mL = 1 g/L which after dividing by 950,000 g/mole = $1.05x10^{-6}$ M. Thus, 0.25 M trehalose/$1.05x10^{-6}$ M IgM = $2.4x10^5$. (d) Then for 15 mg/mL the ratio is $2.4x10^5/15 = 1.6 x10^4$.

Clearly, the molar ratios of trehalose:IgM in Draber *et al.* significantly exceed the presently range of molar ratios of lyoprotectant: anti-HER2 antibody in claims 37 and 42. Moreover, Draber cautions against not including 0.25M trehalose, otherwise the IgM antibodies would have "quickly lost binding activity on 4°C storage or become partially denatured during freezing and thawing" (Draber *et al.*, first paragraph of "Results" on page 39). Applicants submit that reducing the amount of lyoprotectant to the ratios in claims 37 and 42 would not have been considered "routine optimization" of the teachings of the prior art.

The teachings of the other cited references do not supply the deficiencies of Draber *et al.* with respect to the presently claimed molar ratio of lyoprotectant:antibody in claims 37 and 42, or the other aspects of the presently claimed invention.

Reconsideration and withdrawal of the Section 103 rejection of claims

37 and 42, and the claims which depend thereon, is respectfully requested in view of the above.

Applicants turn now to claim 51 which encompasses a method for treating a cancer selected from the group consisting of endometrial, lung, colon, and bladder cancer in a human comprising administering a therapeutically effective amount of a formulation comprising an antibody which binds HER2 receptor to the human, wherein the formulation comprises the antibody in an amount from about 5-40mg/mL, sucrose or trehalose in an amount from about 10-100mM, a buffer and a surfactant.

Applicants first point out that the formulation used in the method of claim 51 (comprising an antibody which binds HER2 receptor in an amount from about 5-40mg/mL, sucrose or trehalose in an amount from about 10-100mM, a buffer and a surfactant) has previously been found to be patentable to Applicants (claim 26[1] of related US Patent No. 6,267,958; of record, which reads "A formulation comprising anti-HER2 antibody in an amount from about 5-40mg/mL, sucrose or trehalose in an amount from about 10-100mM, a buffer and a surfactant"). Moreover, Applicants note that instant claim 29, which also includes this language, is not rejected over the prior art.

Applicants submit that it was not obvious from the cited art that one should, or could, make the presently claimed formulation comprising the species of an anti-HER2 antibody with the recited antibody concentration therein (from about 5-40mg/mL), sucrose or trehalose in an amount from about 10-100nM, a buffer and a surfactant, let alone that such a formulation would be stable as demonstrated in Example 1 of the present application, for instance. Hence, Applicants submit that the formulation in claim 51, and therapy therewith as set forth in that claim, would have been patentable over the cited art at the

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[1] Claim 26 of the '958 patent was patentable over Draber *et al.* relied on in the present rejection.

relevant date.

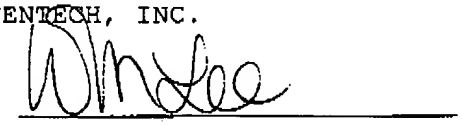
Reconsideration and withdrawal of the rejection of claim 51 is respectfully requested in view of the above.

Applicants respectfully submit that claims 26, 28, 37-43 and 51 are patentable over the cited art, and reconsideration and withdrawal of the Section 103 rejection is requested.

Applicants believe that this application is in condition for allowance and look forward to early notification to that effect. However, if issue(s) remain, Examiner Yaen is invited to call the undersigned at the phone number noted below to discuss any such issue(s), and thereby advance prosecution.

Respectfully submitted,
GENENTECH, INC.

Date: January 8, 2003

By: 

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

26. (Twice Amended) The method of claim 37 [wherein the formulation comprises a lyophilized mixture of a lyoprotectant and the antibody,] wherein the molar ratio of lyoprotectant:antibody is [100-600] 200-600 mole lyoprotectant:1 mole antibody.

29. (Three Times Amended) The method of claim 37 wherein the [fomulation] formulation comprises the antibody in an amount from about 5-40 mg/mL, sucrose or trehalose in an amount from about 10-100 mM, a buffer and a surfactant.

37. (Twice Amended) A method for treating a cancer selected from the group consisting of endometrial, lung, colon, and bladder cancer in a human comprising administering a therapeutically effective amount of a formulation comprising an antibody which binds HER2 receptor to the human, wherein the formulation comprises the antibody and a lyoprotectant, wherein the molar ratio of lyoprotectant:antibody is 100-600 mole lyoprotectant:1 mole antibody.

39. (Twice Amended) The method of claim [51] 37 wherein the cancer is lung cancer.

42. (Twice Amended) A method for treating ductal carcinoma *in situ* in a human comprising administering a therapeutically effective amount of a formulation comprising an antibody which binds HER2 receptor to the human, wherein the formulation comprises the antibody and a lyoprotectant, wherein the molar ratio of lyoprotectant:antibody is 100-600 mole lyoprotectant:1 mole antibody.

43. (Amended) The method of claim 42 wherein [the formulation comprises a lyophilized mixture of a lyoprotectant and the antibody, wherein] the molar ratio of lyoprotectant:antibody is [100-600] 200-

600 mole lyoprotectant:1 mole antibody.

45. (Amended) The method of claim 42 wherein the [fomulation] formulation comprises the antibody in amount from about 5-40 mg/mL, sucrose or trehalose in an amount from about 10-100 mM, a buffer and a surfactant.